REMARKS

I. Status of the Claims

Claims 1-3, 6-15 and 18-25 are pending. Claims 4, 5, 15, 16, 17, and 26-62 are canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to any canceled subject matter.

Claim 1 is amended to recite a method for monitoring the effect of a therapeutic composition on cancer in a mammal and, by performing the recited steps, determining whether the therapeutic composition has an effect on the cancer. Claim 6 is amended to depend from claim 1 and is drawn to colon cancer. These amendments are supported by the specification. See for instance exemplary paragraph 23 ("In a preferred embodiment, the test compound decreases, inhibits, reduces, or downregulates the level of phosphorylated PAK4 in the preparation"); paragraph 40 ("...being able to detect abnormally high levels of such PAKs, especially PAK4, in mammalian samples is useful for identifying compounds that modulate (*i.e.*, inhibit, decrease, downregulate, or reduce) PAK activity"); and paragraph 50 ("The effect of the therapeutic composition on the mammal can therefore be identified by a decrease in the level of PAK phosphorylation after treatment").

Cancelation of claim 15 also moots the objection at page 2 of the action.

These amendments introduce no new subject matter and they furthermore place the claims in condition for allowance. Thus, Applicants respectfully request entry of these amendments.

II. Rejections under 35 U.S.C. §101 and § 112

Claims 1-15 and 18-25 are rejected under 35 U.S.C. § 101. Office action at page 3. The Office contends that "the specification provides no working examples demonstrating that a decrease in PAK4 phosphorylation on ser-474 is indicative of any therapeutic effect. The specification only provides general guidelines or prophetic teaching of how changes in PAK phosphorylation levels *could* be used to monitor an undisclosed effect of a therapeutic composition" (emphasis in original; Office Action at page 4). Thus, according to the Office, "a method of detecting a decrease in phosphorylation of a residue in response to a therapeutic, wherein said decrease is not indicative of anything but a decrease in phosphorylation of said

residue, is not a significant and presently available benefit to the public. Thus, the claimed method does not have a 'substantial' utility." *Id.* at page 5.

Applicants respectfully disagree. Applicants' comments here also apply to the Examiner's rejection of the claims under the "how to use" prong of § 112. In the interest of expediting examination, however, Applicants have amended claim 1 to recite that the method detects the effect of a therapeutic composition on cancer in a mammal. Applicants assert that their observation that the level of PAK4 phosphorylation (on ser-474) decreases when a particular therapeutic composition is administered to an individual who has colon cancer, is exemplary of phosphorylation changes that can be measured in other types of cancers, not only colon cancer. See, for instance, Example 5 of the application.

Applicants reiterate that PAK4 is a kinase that is frequently *overexpressed* in human tumor cell lines of various tissue origins. Please see paragraph 4 of the published application version of the pending case, U.S. 20050054017. Phosphospecific antibodies directed against serine 474 detect activated PAK4 on the Golgi membrane when PAK4 is co-expressed with activated Cdc42. Furthermore, expression of the active PAK4 (S474E) mutant has transforming potential, leading to anchorage-independent growth of NIH3T3 cells. A kinase-inactive PAK4 (K350A,K351A), on the other hand, efficiently blocks transformation by activated Ras and inhibits anchorage-independent growth of HCT116 colon cancer cells. Thus, PAK4 is strongly implicated in oncogenic transformation and suggests that PAK4 activity is required for Ras-driven, anchorage-independent growth. *Id.*

Since PAK4 is an effector for Cdc42, it is most likely associated with chemotaxis, cell adhesion, inflammatory responses, and innate immunological activities. See paragraph 7 of the published application. For instance, there is evidence implicating PAK kinases in oncogenic Ras-driven, anchorage-independent growth and in the regulation of cell survival. *Id.* But no-one in the prior art had thought it useful to use phosphorylated PAK4 as a biomarker for tumorogenesis in biopsy samples obtained from diseased and healthy mammals.

Applicants provide and claim phosphospecific antibodies for monitoring the effect of a therapeutic composition on phosphorylated PAK in mammalian biopsies as well as screening assays to identify compositions that modulate PAK activity. Accordingly, Applicants had the insight to correlate PAK4 phosphorylation levels with cancer state, and to

produce antibodies that recognize specific phosphorylation states of PAK4 and distinguish between two samples from a patient. This knowledge and phosphospecific antibodies can be used to monitor and determine the effectiveness of a candidate anti-cancer drug in modulating the phosphorylation state of PAK4.

In light of this, Applicants had provided exemplary results of the usefulness of the claimed method for monitoring the effect of a therapeutic composition on cancer in a mammal, where they had correlated a decrease in ser-474 phosphorylation levels in colon cancer biopsies after treatment with the therapeutic composition. The effect of this, and other therapeutic compositions, can be ascertained in the same way for the cancers listed in Table 1 of Example 4. See also Example 5 and Applicants' conclusion that a level of phosphorylated PAK4 that is above normal in a certain tissue is a useful biomarker for determining the integrity and status of the cells in the tissue (paragraph 84).

For these reasons, Applicants assert the claimed invention has a well-established and substantial utility for a method of monitoring the effect of a therapeutic composition on cancer in a mammal by measuring the phosphorylation state of PAK4/ser-474 before and after administration of the composition to the individual. The effectiveness of a therapeutic composition to beneficiarily lower phosphorylation levels in individuals with colon cancer is exemplary of this useful method. Applicants therefore respectfully request withdrawal of this Section 101 rejection and the corresponding Section 112, first paragraph rejection, since Applicants' specification does teach how to perform the claimed invention.

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CONCLUSION

Applicants therefore believe this case is in condition for allowance. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.